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*in the  
land  
of the  
blind*

The general practitioner is in a strategic position in the immediate control of cancer. He has the great advantage over his specialist and research colleagues of often seeing the patient at a time when cancer can be cured or even when it can be prevented. As long as the mechanism of malignant changes in the cell remains a mystery and as long as the cure of advanced cancer remains impossible, the most effective efforts toward cancer control are those aimed at recognition and treatment of precancerous and early malignant lesions.

Fortunately for the patient and for the family doctor, practically all of the so-called precancers are accessible and readily diagnosed — keratoses, leukoplakia, moles, fibrocystic mastitis, kraurosis vulvae, cervicitis, cervical erosion, and polyps of the cervix, colon and rectum—all are visible or palpable on the body or mucous surfaces or readily detected by simple speculum examinations.

By his awareness of the precancerous nature of these lesions and by his prompt referral for expert therapy, the general practitioner can perhaps save more lives than can the cancer surgeon or the radiologist.

The programs of cancer research and the gradually improving techniques of surgery and radiology are unlikely to cause any striking immediate change in the cancer control scene. But earlier treatment of cancer and elimination of precancers could.

The family doctor is still king in the blind land of cancer.

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*Cover—*

Pepper, the Dalmatian, in addition to his genetic pigmentation, enjoys another distinction: his is the only class of dog that shares with man the capacity to excrete uric acid as an end product of protein metabolism.



# NEWSLETTER

SEPTEMBER, 1954

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**Chlorpromazine:** Klopp and others (George Washington U.) found that chlorpromazine (a drug that stops nausea and vomiting and controls delirium tremens) gives relief in some kinds of advanced cancer, particularly breast cancer that has metastasized to the liver. Side effects include dehydration but they vary with individuals. When administered with roentgen rays, nitrogen mustard, or acridine, the drug induced distinct subjective relief of symptoms in many cancer patients. The investigators feel that the treatment may lengthen life, but, lacking dependable controls, there is no way of telling for sure.

The same group, in animal experiments, have found an odd role of the liver in some female tumors. They observed, first in women cancer patients, that large doses of aureomycin produced a reversible jaundice and, in some cervical and breast cases, an unexpected degree of palliation. They ligated the bile ducts of rats and mice with spontaneous and transplanted cancers and found that, in females only, regressions occurred while the ligation was effective. After about three weeks the bile ducts again became patent and tumors resumed growth. Indications that the effects were mediated by steroids lay in the fact that some male tumor growth was accelerated by the process.

**Azaserine:** Murphy, Karnofsky, and Roddy (Memorial Center, New York) have reported that a *Streptomyces* product, azaserine, has inhibited sarcoma-180 transplants. At high and toxic doses, the tumors were destroyed completely and resorbed, but the dose that "cured" half the animals killed the other half. Like several other drugs used against cancer, azaserine proved a powerful abortive agent by virtue of its selective action against embryonic tissue. In humans, at safe doses, the preparation has brought slight benefit so far.

**Detection:** Sprunt and others (U. of Tenn.) have taken cervical smears from 70,000 women in the Memphis area in an unprecedented mass examination. On the first go-around, fifteen in every 1000 showed questionable smears that were called to the attention of the family physician.

On biopsy one half of these proved to be cancer; and one half of the cancers had reached the invasive stage. The second go-around is showing far fewer positives. The test, free to residents of Memphis, costs out-of-towners \$5.00. The objective is to take three smears from each of 100,000 women in the Memphis area. Sprunt and his group have experimented with the Penn-Dowdy seroflocculation test and so far have reserved judgment as to its practical value as a blood test for cancer. Sprunt has said, however: "The technique is opening up a new field in experimental medicine--possibly in the field of immunology. It represents the body's response to injury. We do not know yet what this will mean in cancer detection, but it may be extremely interesting as a health clearance test. This is a big contribution to medical science." On the basis of 2000 determinations with three different antigens, Sprunt has noted that the test is undependable in detecting extremely early cancers.

Daraprim: Frost and Jones (Lankenau Hosp. and U. of Penn.) have reported short-term but promising results in polycythemia vera with daraprim, an antimalarial that antagonizes the folic acid--folinic acid system in microorganisms. Developed first as a potential anti-cancer agent, it was picked up and tested by Jones and others in their highly successful search for agents to control malaria among troops in Korea. Tests on twenty-five prisoner volunteers at the Atlanta Federal Penitentiary established safe and effective doses and showed that the drug produced a mild anemia. This led Jones to believe that it might be useful against polycythemia--and it was. The first six polycythemia patients treated with daraprim registered red-cell suppression with no undesirable side effects. The drug also reduced high white cell and platelet counts to normal, but not subnormal, levels. Patients have been maintained in comfort and health for up to one year so far. It is impossible to say whether daraprim will bring long-term results equal or superior to the excellent effects of radioactive phosphorus, which controls the disease for long periods. Daraprim, however, numbers among its advantages its ready availability, the probability that it will be inexpensive, and the fact that its mechanism of action is known (effects are reversible with folic acid). It may take years to determine whether the new drug will eliminate for

(Continued after page 180)



# **C** **a** **Q**

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# Keeping up

## The Diagnostic Problems of Cancer

The burden and major responsibility for the recognition of cancer while it is still curable, still rests, and properly so, in the hands of physicians in private practice, despite the growth and expansion of cancer centers and cancer-detection clinics. Although the more than eight thousand persons a year seen at the Memorial Center Examining Clinic are a selected population known to have or suspected of having some form of tumor or cancer, not a small number of people present themselves with a variety of complaints and symptoms referable to other diseases, and it is not rare to discover presymptomatic cancer in some patients who have come because of unrelated symptoms. Cancer of the breast is the most common cancer encountered and many patients are seen before classical signs develop. In any case of a mass in the breast, or a firm or discrete thickening even in the presence of chronic cystic mastitis, or a nipple rash or discharge, or any suggestion of skin dimpling or axillary adenopathy, pathological verification of the nature of the lesion should be obtained without delay, by biopsy. It is the author's conviction that a benign cervical erosion can not be distinguished from early cancer on sight, and strong emphasis is placed on the danger of cauterizing cervical erosions without first getting microscopic verification of what is being treated. There is no single simple biological test that is a reliable indicator of cancer per se. The general practitioner can best accomplish the change in the outlook on cancer by maintaining a high index of suspicion of cancer, par-

ticularly in older patients, and a determination to attempt to recognize cancer in its presymptomatic stages.

*Houde, R. W.: The diagnostic problems of cancer. J. Michigan M. Soc. 52:1197-1200, Nov., 1953.*

## Cancer of the Lung

Five hundred thirty-two consecutive, histologically confirmed cases of cancer of the lung were seen at the Jefferson Medical College Hospital from April 1, 1946, to January 1, 1953. The histological diagnosis was based in 484 cases on examination of tissue; in the remaining forty-eight cases, on the finding of cancer cells in the bronchial secretions. In about 85 per cent of the patients the roentgenologist correctly made a presumptive diagnosis of bronchogenic carcinoma. Bronchoscopy was performed routinely on all patients in whom bronchogenic cancer was suspected. Since life expectancy has not been greatly extended by any means other than surgical excision, the authors attempted radical extirpation of the cancer in all patients who did not have evidence of spread beyond the limits of the operative field. Exceptions in twenty-two instances were due to refusal to accept surgical treatment by twelve patients and to the presence of other fatal systemic disease in ten. The cancer was removed in 205 of 380 patients (39 per cent) operated on. The whole lung with the regional lymphatic system was removed in 190 instances; lobectomy or bilobectomy was performed in 14 cases. Less than total removal of the lung was done only when there was (1) extensive diminished pulmonary reserve, (2) uncertainty of diag-

# with Cancer



nosis when the lesion was small and peripherally located with no evidence of central extension, and (3) extensive invasion of the thoracic wall by the contiguous cancer. The operative mortality was 22 per cent; the extent of involvement appears to be a significant factor in mortality. In cases in which the tumor extended beyond the lung, the mortality was twice that of the cases in which the mediastinal nodes or contiguous structures were not involved. The five-year-survival rate was 22 per cent for the patients with the cancer removed and 9 per cent for the entire series. Analysis of this and other reported series appears to indicate that the proportion of the total number of patients leaving the hospital alive with the cancer removed is directly related to the proportion of the total number of patients in whom extirpation of the cancer is attempted.

*Gibbon, J. H., Jr.; Allbritten, F. F., Jr.; Templeton, J. Y., III, and Nealon, T. F., Jr.: Cancer of the lung—an analysis of 532 consecutive cases. Ann. Surg. 138:489-496; disc. 496-501, Oct., 1953.*

## Cancer of the Lung in Physicians

Exposures to tobacco and other possible respiratory irritants in sixty-three physicians with cancer of the lung and 133 physicians with cancer outside the respiratory tract were studied to determine the relationship between tobacco smoking and development of bronchogenic carcinoma. It was found that the average age at death for physicians with cancer of the lung was lower than for those with other types of cancer and that patients with cancer of the lung smoked considerably more than the controls of

the same age and economic group, confirming results of previous investigations. Mortality was higher among cigarette smokers than among either pipe or cigar smokers. The estimated mortality from cancer of the lung rose from 10 per 100,000 among nonsmoking physicians to 133 per 100,000 among physicians smoking thirty-five or more cigarettes a day.

*Wynder, E. L., and Cornfield, J.: Cancer of the lung in physicians. New England J. Med. 248: 441-444, March 12, 1953.*

## Diagnostic Tests for Cancer

Dissatisfaction with present methods of cancer detection and treatment accompanies the recognition of need for still further progress. The usefulness of a large number of various procedures as diagnostic tools in cancer detection must be carefully evaluated to satisfy these criteria: reliability, economic feasibility, specificity, and sensitivity. A highly specific differential diagnostic cancer test is the serum acid phosphatase, which is elevated in cases of prostatic cancer provided the tumor has grown beyond the prostatic capsule and phosphatase reaches the blood stream. Other procedures considered useful for differential diagnosis are: serum alkaline phosphatase (osteogenic sarcoma), Bence Jones protein in blood and urine (multiple myeloma), adrenal steroids in urine (adrenal tumors), pituitary or chorionic follicle-stimulating hormone in urine (testicular tumors), disturbance of clotting mechanism of blood (pancreatic tumors), melanin precursors in urine (melanoma), selective localization of radioiodine (thyroid tumors), deficient enzyme levels in

pancreatic juice (pancreatic tumors), gastric analysis (stomach tumors), and cytology (tumors of gynecological, respiratory, intestinal, and urinary tracts). Procedures considered useful for screening for specific tumors are: cytology (Papanicolaou smears in carcinoma of cervix), occult blood in feces (gastrointestinal cancer), detection of hematuria (genitourinary cancer), and hematology (leukemia). Caution on the part of the physician faced with the problem of diagnosis of cancer before he accepts any new "test" is recommended.

Homburger, F.: *The present status of "cancer tests."* J. Michigan M. Soc. 52:267-273, March, 1953.

### Cervical Carcinoma in Situ

Routine cervical biopsies should be done periodically in order to increase the number of cervical carcinomas detected while still amenable to treatment. Histological examination of excised cervical tissue still remains the most reliable diagnostic aid. Any case showing unmistakable dissolution of the basement membrane or the slightest degree of stromal invasion may not be classified as in situ carcinoma. One case of carcinoma in situ was found among 4152 cervical biopsy specimens. Circular biopsy is preferable to single or multiple "spot" biopsies. There should be a central body qualified to review all diagnoses of carcinoma in situ.

Hoffman, J.; Farrell, D. M., and Hahn, G. A.: *Review of 4,152 biopsies of the cervix with relation to carcinoma in situ.* J.A.M.A. 151:535-540, Feb. 14, 1953.

### Prognosis of Surgical Treatment of Gastric Cancer

In order to determine the factors that influence the prognosis following surgical treatment of gastric cancer, two groups of patients, consisting of thirty-four patients who survived five or more years after gastric resection for carcinoma of the stomach with notable metastasis and thirty-four similar patients who died within one year after operation, were compared. The duration of symptoms among the long-term survivors was nearly three

times as great as that among the short-term survivors. Gastric retention occurred oftener among the short-term survivors, but anemia was less common in the short-term group. The authors recommend that a satisfactory operation for gastric cancer should include (1) total removal of the lesion and any local extension of it; (2) resection of the stomach at least 4 or 5 cm. beyond the zone of microscopic extension; (3) complete removal, as far as possible, of any avenues of lymphatic spread; (4) removal of gastrohepatic and gastrosplenic omenta, greater omentum, and often the spleen; and (5) resection of a portion of the esophagus or duodenum if the lesion approximates these structures. Although opinion differs regarding the advisability of total gastrectomy, the authors believe that in most cases the removal of areas of lymphatic drainage can be carried out just as extensively if the stomach is subtotally resected. Since the mortality and morbidity from total gastrectomy are higher than for subtotal resection, they do not employ total gastrectomy routinely in the treatment of all patients with cancer of the stomach.

ReMine, W. H.; Dockerty, M. B., and Priestley, J. T.: *Some factors which influence prognosis in surgical treatment of gastric carcinoma.* Ann. Surg. 138:311-319, Sept., 1953.

### Neoplastic Spread

Roentgen-ray studies of the lungs and major red-bone-marrow areas should be made of all patients with cancer of the breast, prostate, kidney, lung, thyroid, bone, or testicle, since these growths often have metastatic extension. The most consistent pattern of bone lesion secondary to malignant tumor appears with cancer of the prostate. Spread is probably through the rich regional perineural lymphatics. Epidermoid carcinoma, if metastatic to bone, almost always produces osteolytic metastases. Spread of breast cancer by direct extension to the pleura of the same side of the chest, producing pleural effusion and further dissemination, is a prevalent pattern. Lung metastases secondary to cancer of the colon and pulmonary foci of lymphoma may cause hemoptysis. If

a metastatic focus originates near a large bronchus, complete atelectasis of a lobe may occur. Search of sputum for metastatic tumor cells is desirable on the basis of roentgenological and clinical signs of bronchial communication from secondary foci in lungs as well as from primary foci. The radiologist should make every attempt to discover solitary metastatic nodules that can be removed. To select patients for surgical therapy, the following criteria may be applied: the primary growth should be controlled; the primary lesion should be a well-differentiated type of tissue; the interval between control of the primary growth and first recognition of the metastatic focus should be longer than a year. The more complete the histological differentiation and eradication of the primary growth and the longer the period of time before metastatic foci appear after the first lesion is treated, the more favorable the prognosis of palliative resection. Intensive radiotherapy should be used for localized metastatic disease not amenable to surgery. Hormone-level alteration may be combined with radiotherapy. Radical surgery for relatively early widespread metastatic disease from cancer of the lungs, stomach, or pancreas gives disappointing results. Still earlier diagnosis of primary cancer is essential.

Turner, J. W.: *Observations on neoplastic spread; some radiologic aspects of the problem.* *New England J. Med.* 249:507-514, Sept. 24, 1953.

### Gastric Ulcer and Carcinoma

A group of 411 consecutive cases of gastric ulcer in which surgical resection was performed is reported. Three hundred forty-six cases were benign ulcers and sixty-five proved to be malignant ulcers. Malignant transformation of gastric ulcer sometimes will occur, but the greater danger lies in treating an unrecognized cancer medically, since ulcerating carcinomas may cause symptoms indistinguishable from those of benign ulcer. If medical management is advised, the gastric ulcer must be watched by repeated roentgenological and gastroscopic examinations.

The only reliable evidence of a healing benign ulcer is disappearance of occult blood from the stools and of the ulcer crater as shown by roentgenograms and gastroscopic examinations. If the ulcer recurs, surgical resection is mandatory. The only safe course is insistence upon surgical excision if healing is not complete at the end of an adequate period of controlled therapy. Gastric ulcer visible on the roentgenogram and characteristic in every way of benign ulcer proves to be cancer in at least 10 per cent of cases. In many cases, differentiation must be made by pathological examination after removal of tissue. Immediate operation in every case of gastric ulcer is not advocated but it is the author's opinion that a higher percentage, probably 50 per cent or more, of chronic gastric ulcers should be resected, since an appreciable number (15.8 per cent) have been found at operation to be malignant.

Marshall, S. F.: *The relation of gastric ulcer to carcinoma of the stomach.* *Ann. Surg.* 137:891-903, June, 1953.

### Etiology of Carcinoma of the Lung

The results of a large-scale investigation to determine whether smoking or atmospheric pollution could be responsible for the development of carcinoma of the lung are reported. Nearly 5000 hospital patients were interviewed between 1948 and 1952 in five specific areas of inquiry. The data analyzed tend to the conclusions that pipe smoking, although also related to carcinoma of the lung, appears to carry a smaller risk than smoking cigarettes; the use of cigarette holders is associated with a somewhat smaller incidence of lung cancer than nonuse of such holders; the smokers who use filter-tipped cigarettes have a lower comparative incidence than smokers who do not use filter-tipped cigarettes; no difference is apparent in the incidence of carcinoma among those smokers who inhale and those who do not, and no significant difference was noted between those who smoked hand-rolled cigarettes and those who smoked "tailor-mades." In regard to the histological type



of carcinoma, there were too few proved cases of adenocarcinoma to permit statistically accurate conclusions. Of the 1357 men with lung cancer, 4 per cent had adenocarcinoma, whereas of the 108 women with malignant tumors of the lung, 13 per cent had adenocarcinoma. The incidence of epidermoid carcinoma in men was about twice that in women, while anaplastic or undifferentiated carcinomas were more evenly distributed. The authors conclude that smoking is a factor, and an important factor, in the production of carcinoma of the lung.

Doll, R., and Hill, A. B.: *A study of the aetiology of carcinoma of the lung. Brit. M. J.* 2:1271-1286, Dec. 13, 1952.

### Occupational Factors in Lung Cancer

This exploratory study of the occupations that have a suggestive association with lung cancer is intended as a preliminary analysis. To obtain further data on the etiology of lung cancer, the California State Department of Public Health has investigated the occupational and smoking history of a group of lung-cancer patients and of a control group. The lung-cancer series and the control group were equated as to age, sex, race, and socioeconomic status. Preliminary analysis of the data for 408 lung-cancer patients and 408 controls confirms the association between excessive cigarette smoking and lung cancer identified in previous studies. Five occupations were selected because the number of lung-cancer cases exceeded by several times the number of control cases and because exposure to certain metal fumes and particles was common among the five occupations. Individuals employed in these occupations: welders, crane-men and derrickmen (exposed to metal fumes), firemen (stationary and marine boilers), metal miners (copper, lead, and zinc), drillers and tool dressers (oil),

should be studied intensively to determine the etiological factors involved.

Breslow, L.: *Occupational factors in lung cancer; a preliminary report. Pub. Health Rep.* 68:286-288, March, 1953.

### Detection of Unsuspected Gastric Neoplasms

A review of the authors' experiences with the 70-mm. photofluorograph for the screening of unsuspected gastric lesions in 5341 patients is presented. In this group of relatively asymptomatic patients of 40 years or older, 322 persons required further examination and, among these, eleven "concealed" gastric neoplasms were found. Three proved to be carcinoma at operation; one probable carcinoma was not considered operable because of a coexisting cardiac abnormality. Five patients had proved benign adenomas of the stomach, and in two additional cases a diagnosis of adenoma was made but surgery was refused. A considerable amount of space is devoted to financial considerations and when estimating the costs for uncovering a single gastric carcinoma, one must not lose sight of the fact that, while discovering this one cancer, there have been uncovered an average of three other gastric neoplasms, each adenomatous polyp carrying a fairly high probability of being or becoming malignant. A discussion of the incidence of carcinomas and other stomach lesions as reported by others, with an extensive review of the literature, is presented. It is concluded that photofluorography offers a reliable method of detecting unsuspected gastric neoplasms and at least one of its precursors at a more favorable period for surgical treatment in large population groups.

Wigh, R., and Swenson, P. C.: *Photofluorography for the detection of unsuspected gastric neoplasms. Am. J. Roentgenol.* 69:242-266; disc. 266-267, Feb., 1953.



a glance . . .

one-minute abstracts  
of the current literature  
on cancer . . .

### **Villous Papillomas of the Colon and Rectum**

Benign epithelial polyps arising from the mucous membrane are the most common tumors of the colon and rectum. Of these, the more common are the adenomatous polyps, typically compact pedunculated masses having a papillary arrangement of the luminal pole. These occur in about 7 per cent of all adults and become malignant in 15 to 19 per cent of cases. The other less common type occurs as a lesion with a broad, sessile, velvet-like appearance containing soft, villous projections, in striking contrast to all other benign or malignant tumors of the large bowel. Villous papillomas often present a problem, for repeated biopsies of lesions may show a benign lesion and they cannot be excised early locally or desiccated as can the adenomatous polyps. Villous papillomas present symptoms that may be confused with mucous colitis, including a mucous discharge from the rectum. Other symptoms include rectal bleeding, altered bowel habits (especially diarrhea), and the protrusion of tissue. The duration of symptoms of the cases reported varied from one week to fifteen years, the average being fifteen months.

Malignant changes were found in 35.7 per cent of the papillomas in this series. Recognition of villous papilloma, from the criteria described, and appreciation of its tendency toward malignant behavior present indications for adequate extirpation of involved large bowel and areas of lymphatic drainage despite ostensibly benign pathology.

*Bacon, H. E.; Lowell, E. J., Jr., and Trimpi, H. D.: Villous papillomas of the colon and rectum; a study of twenty-eight cases with end results of treatment over a five-year period. Surgery 35:77-87, Jan., 1954.*

### **Polyps and Adenomas of the Stomach**

Thirty-one of sixty-nine patients with benign gastric adenomas were asymptomatic. Only one of twenty-eight patients with cancer was asymptomatic. Achlorhydria is present in 85 to 90 per cent of patients with gastric adenomas. Gastric analysis is a satisfactory screening test for the selection of patients for roentgenological and gastroscopic examination for gastric adenomas. Most of these occur in association with a chronic atrophic gastritis. There is no difference in the gross histological morphology of adenomas occurring singly or in adenomatosis. Sub-

total gastric resection performed in patients with benign adenomas and a severe atrophic gastritis may be followed by pernicious anemia. Anaplastic changes appear to be more common in the cells of the adenomas associated with and containing cancer than in those in which no cancer exists. Small gastric adenomas are much less likely to be malignant than large ones. The size of adenomas is probably the most valid single criterion for determining the malignancy of the growth. Carcinomatous change in benign adenomas does occur. Observation management of patients diagnosed as having small benign lesions is justified if they can be observed at frequent intervals.

Hay, L. J.: Polyps and adenomas of the stomach. *Surgery* 33:446-467, March, 1953.

### Soft-Part Tumors

Although the development of malignant tumors from benign tumors is extremely rare, there should be an awareness of the possibility of occurrence. The thigh (including the gluteal and inguinal regions) and the retroperitoneum are the two most frequent sites of soft-part tumors, fibrosarcomas occurring most frequently in the thigh and liposarcomas and leiomyosarcomas most frequently in the retroperitoneal area. Synovial sarcomas are limited almost exclusively to the extremities. Surgery with certain assistance from radiotherapy is considered the only method of treating this group of neoplasms, after biopsy is performed. Causes for the poor over-all salvage rate of this group of tumors are attributable to: delay in diagnosis (culpability for delay usually lay with the patient in those instances in which a painless mass existed and with the physician when pain and no apparent mass existed) and inadequate surgical intervention without biopsy. It was felt that marked improvement in prognosis could be attained by earlier diagnosis and the institution of more radical surgery.

Stout, A. P., Moderator: Panel on soft-part tumors. In *Proceedings of the First National Cancer Conference*. [New York.] American Cancer Society, Inc. 1949; pp. 206-216.

### Benign and Malignant Gastric Ulcer

Benign gastric ulcer of the greater curvature is rare. A review of gastric ulcers removed surgically reported by Allen and Welsh states that in their series 100 per cent of the ulcers of the greater curvature were malignant. A comparison of the incidence of benign and malignant ulcers of the greater curvature is made. Of eighteen ulcers of this type that were seen on two hospital services and in private practice, ten proved to be malignant and eight benign on pathological examination. Benign ulcer of the greater curvature is frequently found in association with duodenal ulcer or benign ulcer of the lesser curvature of the stomach. The authors believe that the finding of such ulcers in more than one location favors a benign origin of the greater-curvature ulcer. They remark upon the curious fact that, of eight benign greater-curvature ulcers, three were associated with primary pulmonary carcinoma and that in each of the three instances death was due to gross hemorrhage from the ulcer. In addition to other clinical methods, gastroscopic examination is an important adjunct in the differential diagnosis of benign and malignant ulcer of the greater curvature, since the greater curvature is readily accessible to gastroscopic observation.

Silk, A. D.; Blomquist, O. A., and Schindler, R.: Ulcer of the greater gastric curvature. *J. A. M. A.* 152:305-307, May 23, 1953.

### Polyps of the Colon

Most authorities now agree that a polyp in the large intestine is a signal of danger. Swinton and Warren have reported a study of 156 patients who had so-called benign polyps and announced that all stages in the sequence of change from normal mucosa to adenocarcinoma could be demonstrated histologically. The authors are of the strong persuasion that a colon in which polyps are prone to form serves warning that it is also a colon in which carcinoma is prone to form. A review of 246 patients followed five years or more after transcolonic removal of a

polyp is presented. The over-all result was that 72 per cent showed no further polyps; 15 per cent developed polyps requiring abdominal operation; and 13 per cent, polyps that could be treated through the sigmoidoscope. There were fifteen recurrences that were malignant. There were twenty-eight deaths in those in whom there was no known recurrence; two were due to "cancer, site undetermined." The association of "sentinal polyps" in the same specimen with "full blown" colonic cancers has been striking; possibly the presence of two or more polyps renders the patient who harbors them more susceptible to the development of cancer. The necessity for twenty-year or thirty-year follow-ups on these patients is stressed, as nearly a third of the recurrences appeared after five years. Because of the tendency to recur in the distal sigmoid and rectum, the authors believe more consideration should be given to the so-called low anterior resection for polyps in this area. Also, where two or more polyps are found close together, extensive segmental resection or subtotal colectomy should be considered. Since more than 50 per cent of those polyps in which microscopic evidence of invasion of malignant cells was present recurred as clinical carcinoma, it is concluded that such polyps should be treated originally as definite carcinoma.

Judd, E. S., Jr., and Carlisle, J. C.: Polyps of the colon; late results of transcolonic removal. *A. M. A. Arch. Surg.* 67:353-362, Sept., 1953.

### Asymptomatic Adenoma of the Bronchus

The common type of adenoma produces signs of airway obstruction, such as productive cough, fever, chills, and hemoptysis. However, approximately 23 per cent of adenomas occur without atelectasis and the lesions are discovered incidentally. A roentgenogram of the chest reveals a sharply circumscribed round or oval mass of homogeneous density, and as such it does not differ from the opacities produced by some bronchogenic cysts, inspissated abscesses, bronchogenic

carcinomas, single metastatic malignant nodules, granulomas, and noncalcified hamartomas. Bronchial adenoma may exist for years without causing significant symptoms and early resection may prolong life. The operation is more difficult and the incidence of complications after surgery is greater if bronchi are obstructed long enough for suppurative disease to develop distal to the obstruction. Total removal of the mass may require only a segmental resection or a pneumonectomy. Recurrence or metastasis of the lesion is uncommon. Examination of the resected specimen usually reveals an adenoma of the carcinoid variety. All circumscribed masses in the lung, if not calcified or metastatic, should be surgically excised, even though the patient has no respiratory symptoms.

Good, C. A., and Harrington, S. W.: Asymptomatic bronchial adenoma. *Proc. Staff Meet., Mayo Clin.* 28:577-586, Oct. 21, 1953.

### Benign Tumors of the Esophagus

Fifteen cases of benign esophageal tumors are presented, including nine leiomyomas, two cysts, two fibromas, one polyp, and one hemangioma. The diagnosis was correctly determined in eleven patients; in one of the other four patients, a fibroma was confused with an intrathoracic goiter. Benign esophageal tumors can be diagnosed with assurance by means of the barium swallow and fluoroscopy. A biopsy, by breaking through the mucosa, may add greatly to the risk of removal of an esophageal tumor. Esophagoscopy was performed in nine patients, and the benign nature of these tumors was recognized by direct vision, thus eliminating the need for a biopsy. In this series, some special problems were encountered, necessitating use of several different approaches, but the majority of these tumors can be removed by thoracotomy with enucleation of the tumor without incising the esophageal mucosa. The intraluminal tumors can be removed safely through the esophagoscope with the snare and the coagulating current, provided the tumor is not too large or its pedicle too broad.

In fourteen of the total fifteen cases, the tumor was successfully removed surgically; the hemangioma was not treated surgically. There were no deaths in the entire group, and follow-up study reveals no recurrence of symptoms.

Boyd, D. P., and Hill, L. D., III: *Benign tumors of the esophagus*. *Ann. Surg.* 139:312-324, March, 1954.

### Silent Carcinoma of the Cervix

While most emphasis has been placed on the usefulness of the Papanicolaou smear as a screening procedure in cancer-detection clinics, this technique also has an important role in the office practice of both the specialist and general practitioner. There were 383 patients examined in the office during a sixteen-month period, in five of whom a diagnosis of "unsuspected" cancer of the cervix was made by Papanicolaou smear. The cases examined were for the most part those of minor cervical lesions, such as erosions, polyps, chronic cervicitis, and abnormal vaginal bleeding. The diagnosis by Papanicolaou smear was confirmed by biopsy in all five cases: two cases of early invasive carcinoma of the cervix and three of carcinoma in situ. More extensive use of this method in the office practice of the general practitioner as well as the specialist is strongly recommended, since the early diagnosis of carcinoma of the cervix still remains the most important weapon in lowering mortality from this disease.

Wright, R. C., and Bristol, D. A.: *Detection of clinically unsuspected carcinoma of the cervix in office practice by the vaginal smear*. *Connecticut M.J.* 16:162-163, March, 1952.

### Diagnosis and Treatment of Melanoma

Congenital pigmented nevi are seldom the source of malignant melanoma. Rather, lentigo maligna, an acquired smooth brown lesion with collections of premalignant cells at the epidermodermal junction is most apt to give rise to the disorder. Blue-black or slate-gray moles are already malignant. Lentigo maligna can

be differentiated from the benign acquired nevus by the following points: size of the macule, continuing change in growth or regression, frequent grouping of several spots by apposition of new elements, chronic plasma-cell inflammation and atrophy, and eminent disposition to melanoma formation. Malignant anaplastic cells contain a higher degree of anaplasia than do nevus cells and, in addition to penetrating the dermis, are cast off at the cutaneous surface. With lentigo maligna, a slight to pronounced lymphocytic infiltrate is seen in the superficial dermis. This infiltrate is found in nevi only when infected and to a slight degree in seborrheic persons. Because of the asymptomatic nature of melanoma, biopsy should be made of all pigmented cutaneous lesions.

Becker, S. W.: *Pitfalls in the diagnosis and treatment of melanoma*. *A. M. A. Arch. Dermat. & Syph.* 69: 11-30, Jan., 1954.

### Carcinoma of the Female Genital Tract

Immediate attention should be accorded conditions that predispose to cancer: chronic endocervicitis as such or combined with erosion, laceration, inflammatory infiltration, cystic transformation, leukoplakia, or polyps. There should be frequent follow-up examinations to disclose recurrences. If the menopause is delayed, there should be diagnostic curettage. Cells in the stage of division, as in hyperplastic endometrium, are particularly susceptible to the effect of cancerogenic agents. The author prefers vaginal hysterectomy and bilateral salpingo-oophorectomy to cause cessation of the faulty ovarian function. Since approximately 60 per cent of ovarian carcinomas develop from cystomas, especially papilliferous cysts, such formations should be excised. Education of the public by advocating periodic examination is of exceeding importance in the prevention of cancer of the female organs.

Amreich, I.: *Prophylaxe des Genitalkarzinoms*. [*Prophylaxis of carcinoma of the female genitalia*.] *Wien. med. Wchnschr.* 102: 320-325, April 26, 1952; from *abstr. in Internat. Abstr. Surg.* 96: 151, Feb., 1953.



# The Differential Diagnosis of Benign and Malignant Pelvic Lesions in Women

Warren R. Lang, M.D.

All physicians are constantly faced with the problem whether or not the symptoms and clinical findings of a given patient are on a benign or malignant basis. This is especially true in gynecological problems, since the female generative organs are the most common site of malignant tumors in women. It is therefore fitting to review briefly the common benign lesions and mention how a differential diagnosis is made between these and their malignant counterparts. A list of the methods available is given in Table 1.

## Cervix

Erosion is the commonest abnormality of the uterine cervix. It presents itself clinically as a more or less regularly outlined red area with a smooth or finely granular base at the periphery of the cervical os. Erosions may be congenital but more often they are acquired, resulting from infection or childbirth. Early cervical cancer is indistinguishable to the naked eye from a so-called erosion yet a differentiation between the two must be made. Any erosion is suspect that bleeds easily on touching, even in a young woman; or that seems to be more extensive than previously; or that heals poorly after cauterization; or that occurs in an older woman at a time of life when the genital tissues should be quiescent. Adequate biopsy is the only certain method of determining the true nature of an "erosion" in such an instance. In questionable case a circular (annular, cone, ring) biopsy accompanied by fractional curettage is done as a hospital procedure. Of accessory means of diagnosis, the cytological smear is most valuable. Since carcinoma is one of several conditions in which staining does not occur with aqueous iodine

TABLE 1

## Methods of Diagnosis of Gynecological Cancer

- |                             |                            |
|-----------------------------|----------------------------|
| 1. History                  | 7. Sponge biopsy           |
| 2. Pelvic examination       | 8. Roentgenography         |
| 3. Cytological smear        | 9. Colposcopy              |
| 4. Biopsy                   | 10. Endoscopy (culdoscopy) |
| 5. Dilatation and curettage | peritoneoscopy)            |
| 6. Schiller's test          | 11. Laparotomy             |

solution (Schiller's test), this method may be used to locate the desirable site of biopsy. Sponge biopsy and colposcopy (inspection of the cervix under magnification) are not widely used in this country.

Friable cervical polyps present the same symptom as cervical cancer, namely, contact (traumatic) bleeding. Although rarely malignant in themselves, concomitant endometrial carcinoma occurs frequently enough in older women so that polypectomy must of necessity be combined with curettage.

There are bound to be occasions when the clinician receives a histopathological report of carcinoma *in situ*; more tissue should then be obtained for study. Such a diagnosis during the prepartal period calls for repeat evaluation after delivery before definitive treatment can be decided upon.

## Corpus

Most errors in the diagnosis of corpus (endometrial, fundal) carcinoma are made during the menopausal era, when irregular uterine bleeding occurs. While this bleeding may be dysfunctional, it is safest to curette such patients if the pe-

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riods do not tend to become scantier and less frequent. Postmenopausal bleeding signifies cancer in almost 50 per cent of cases; it can NEVER be assumed to be "dysfunctional."

There is an important syndrome of findings known as fibrosis uteri. This is characterized by prolonged menstrual bleeding, sometimes metrorrhagia, at the end of the menstrual life in multipara. The uterus is boggy and often retroverted. Curettage is necessary to differentiate this syndrome from corpus cancer.

Fibromyomas are the most frequent benign tumors of the corpus. Their chief symptom is progressive menorrhagia. The diagnosis is ordinarily not difficult by pelvic examination, but one cannot always be sure that the mass is not adnexal in origin. It should be recalled that about one third of the cases of endometrial cancer are complicated by myomas. When myomas grow rapidly, sarcomatous degeneration should be seriously considered.

### **Ovary**

Although the exact nature of an ovarian enlargement is determined only by the microscope, there is one group of cystic tumors that may be observed by careful, repeated pelvic examinations. These are the so-called non-neoplastic cysts (follicular and luteal) that represent variants of normal physiological changes. The chief findings are menstrual irregularity, perhaps unilateral lower-quadrant discomfort, and a cystic swelling up to 5 cm. in diameter. They characteristically decrease in size after one or two menstrual periods. Should progressive enlargement occur, laparotomy is necessary. Every adnexal enlargement in older women requires surgical exploration.

Ovarian carcinoma in its advanced stages with cachexia, pain, abdominal enlargement, and pelvic masses is readily detected, but occasionally one sees the triad of ascites, hydrothorax, and pelvic tumor

when removal of a benign neoplasm, usually a fibroma, serves to cure the patient of her difficulties (Meigs's syndrome). It is mainly for this reason that the abdomen should be opened in every case of presumed ovarian cancer.

### **Vulva**

Such benign conditions as leukoplakia, lymphopathia venereum, and granuloma inguinale are known to precede vulval cancer and should be treated and then observed periodically. If ulceration occurs in any of these lesions or de novo, biopsy should be performed. Pruritus vulvae, a syndrome of many causes, is an early herald of vulval cancer. Although the vulva is an accessible area to examine thoroughly, it often is not even inspected by many physicians; hence the average delay period of more than eighteen months in the treatment of this disease.

### **Vagina**

The vagina is principally subject to various inflammatory processes that at times are accompanied by ulceration. Should such be found, especially in older women, a piece of tissue from the edge of the ulcer should be studied histologically. With so-called senile vaginitis, care should be taken to determine the actual source of bleeding and, if there is doubt, a dilatation and curettage and cervical biopsy performed; otherwise the true diagnosis of uterine cancer will be delayed.

### **Fallopian Tube**

As with the vagina, the most common tubal lesions are inflammatory, existing in women of the reproductive age group. Adnexal enlargements in later years, with pain and slight serosanguineous discharge, suggest tubal carcinoma. However, the diagnosis of this rare entity is seldom made preoperatively.

# Differentiation between Benign Prostatic Enlargement and Prostatic Cancer

*Perry B. Hudson, M.D.*

Benign prostatic enlargements are, in the main, caused by hypertrophy or hyperplasia and sometimes by a combination of the two processes. Prostatic cancer for practical purposes is adenocarcinoma. As far as is known, the benign enlargements do not undergo malignant degeneration or change. However, the two kinds of tumor—benign and malignant—occur in the same racial and age groups among the total male component of populations. They may, and frequently do, occur in the same patient. This coexistence of the two diseases would, at first glance, appear to create a state of confusion in the minds of practical clinicians. The opposite is the actual case.

The main reason that it is fortunate to find coexistent benign prostatic enlargement and carcinoma is that early adenocarcinoma of the prostate gland produces no characteristic symptoms that the patient may report to his physician. This is readily understandable when one considers that the vast majority, if not all, prostatic malignant tumors originate in the posterior prostate. A malignant tumor growing in this region must attain considerable proportions or must directly invade the urethral lumen before urinary symptoms that are commonly described as "prostatism" develop (Fig. 1).

Benign prostatic enlargements begin in what is properly termed the periurethral glandular prostatic tissues and often, rather early in the course of their development, encroach upon the urethral lumen and produce either symptoms or an increasing residual urine.

When both benign and malignant prostatic tumors are growing simultaneously in the same patient, the symptoms that most often bring the patient to his physician for assistance and advice are those

caused by the benign tumor, and it is at this point that the greatest opportunity is gained for diagnosis of the underlying early prostatic cancer (Fig. 2).

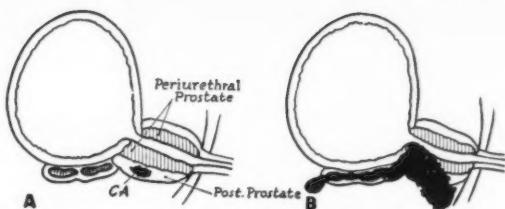
Physical examination is the time-honored method for detecting early prostatic cancer at a curable stage in the course of the disease. The characteristic differences between benign and malignant prostatic tumors from rectal-palpation findings are great enough to warrant consideration (Fig. 3). However, in order to detect early prostatic cancer by this method of rectal palpation, it is necessary to perform palpatory examinations at not more than six-month intervals in males after the age of 50 years—those who are symptom-free as well as the ones who have developed minimal or moderate prostatism. The finding of a suspiciously hard area in the prostate gland or a single indurated nodule is evidence enough to warrant surgical biopsy of the gland. It is only by this means that the earliest lesions can be detected and curative measures instituted. Tissue diagnosis of some sort, preferably by open surgical biopsy of the gland through the perineal surgical route, must provide the definitive diagnosis upon which any form of treatment is based. Many early prostatic cancers do not become indurated and are not suspected at rectal examination.

The surgical specimen from conservative prostatectomy of any type does not contain a sampling of the posterior prostate, in which most of the malignant neoplasms arise. Prostatic surgery performed for what is presumed to be a benign enlargement will result in a surgical pathological specimen that can give no assur-

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FIGURE 1. A, Small localized prostatic cancer—no symptoms. B, Prostatic cancer developed to a point of direct extension into surrounding tissues—therefore incurable—with barely enough encroachment upon the urethral lumen to cause first symptoms of urinary frequency and nocturia.



ance to the operator that cancer does not exist in the posterior prostate (Fig. 4).

The punch or needle biopsy of the posterior prostate, a method that is at the moment receiving renewed attention from clinicians, is useful in detecting prostatic cancer under the proper circumstances. In the main, this technique is useful for those tumors that are strongly suspected at rectal palpation, as well as for those that are

thought with a fair degree of certainty to be incurable. In the latter instance the punch-biopsy specimen is of value in providing a sound basis for the institution of immediate hormonal control measures—castration and the administration of estrogenic substances. In the case of suspected "curable" cancers, the punch biopsy should be disregarded if the tissue examined reveals no carcinoma. There is no reliable means of determining that the indurated area in the prostate felt at rectal examination was actually biopsied with the punch instrument. In the event of an indurated prostatic nodule that is negative to punch biopsy, open perineal prostatic biopsy is the logical recourse for confirmation or correction of this diagnostic impression.

The final differential diagnosis of early prostatic cancer, and especially the differentiation from benign prostatic hyperplasia or hypertrophy, is a tissue diagnosis, not one that can be obtained from medical history, physical examination, or even laboratory tests.

The only laboratory tests that are diagnostic of prostatic cancer are those that reveal cancer in its metastatic phase. These

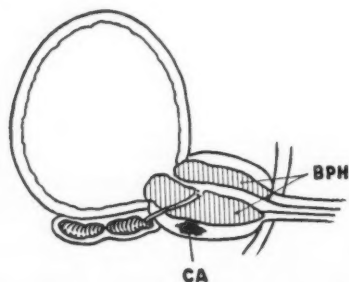


FIGURE 2. The large, benign periurethral prostatic tumor (BPH) shown here brings the patient to his physician through the production of severe "prostatism." The coexistent cancer in the posterior prostate, which may or may not be indurated, is discernible only by biopsy.

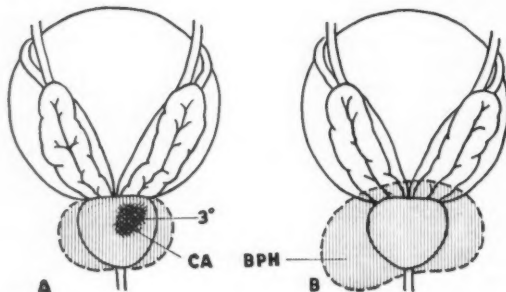
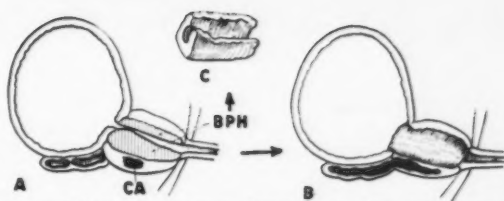


FIGURE 3. A, The size of the prostate is not relevant to the palpation impression of cancer. The "third degree induration" noted by the examiner is, in itself, enough to require biopsy. B, Although the prostate is greatly enlarged, there is no area in the gland that is more suspect of being cancerous than any other. However, routine biopsy before definitive surgery will reveal cancer in about 15 per cent of prostates of this sort.

FIGURE 4. A, Small circumscribed cancer still confined within the limits of the anatomical prostatic capsule. There is also coexistent benign prostatic enlargement of the periurethral glands. It is the latter condition that prompts surgical removal of the periurethral tissue—in this instance without biopsy of the posterior prostate. The surgical pathological specimen shown in C does not contain a sample of the posterior prostate; tissue diagnosis is therefore of a benign nature only. B, Postoperative relief of obstruction from benign tumor. An unsuspected cancer in the posterior prostate is beginning to spread.



tests are: (1) elevated serum-acid-phosphatase levels; (2) radiographic evidence of metastases, especially osteoblastic lesions; in the lumbar spine, pelvis, and densities in the thoracic roentgenogram; and (3) the finding of cancer cells in specimens from bone-marrow aspiration.

Obviously, the greatest opportunity for utilization of tissue diagnostic methods comes at the time of elective surgery to relieve prostatic obstruction caused by what is believed to be a benign enlargement. Routine surgical biopsy, carefully performed, does not produce disturbances in either urinary control or sexual potency.

If routine surgical biopsy were performed throughout the United States—prior to the selection of a definitive operation for all patients in whom prostatic surgery of some sort is necessary—then more patients with early, operable prostatic cancer could be offered definite hope for cure within six months than have been in the fifty years since a curative operation was first devised.

Curative operations for early prostatic cancer are, even today, infrequently performed. The techniques of total prostatectomy by both perineal and retropubic surgical approaches are, however, gaining in popularity. To those who persist in the pessimistic attitude that prostatic cancer is incurable and should be "managed" by hormonal measures alone, it should be pointed out that the widespread utilization of hormonal control measures for more than a decade in the United States has not produced a decrease in the death rate from this disease. There is a continuing annual increase in deaths from prostatic cancer. This annual increase may be anticipated for as many years as may be required to convince clinicians in general that ablative surgery offers the only hope of cure for prostatic cancer. The tissue diagnostic methods required for accurate establishment of the diagnosis of prostatic cancer are not new. The surgical-biopsy techniques can easily be learned and safely applied.

#### On the Cover of the July Issue of CA

The legend for the cover of the July issue stated that Mt. Rubidoux was in the background. Actually the cover shows the Box Springs Mountains and the distant San Bernardino Mountains that rise behind the city of Riverside. The photograph was taken from Mt. Rubidoux.



# Benign Lesions of the Breast

*Kenneth E. Fry, M.D.*

The physician, general practitioner, or specialist must advise patients with breast tumors as to proper management. It is surprising that Leach and Robbins found that 50 per cent of these patients received "improper advice" and in Haagensen's study 27 per cent were given "wrong medical advice." Each year in the United States more than 50,000 women develop breast cancer, but a frequently overlooked fact is that at least an equal number develop benign breast disease requiring surgery. This latter group deserves the same care, attention and good advice as does that with malignant tumors.

The previous excision of benign disease of the breast does not exclude the presence of cancer, for 8.6 per cent of patients having had surgical treatment for benign disease later developed breast cancer.<sup>2</sup>

## Self-examination

Self-examination of the breasts by the patient at least once every month and periodic or confirmatory examination by the physician may eventually result in finding tumors so small that differentiation by physical examination between benign or malignant disease will not be possible. This point has not been reached at the present time.

## Inflammation

Inflammatory lesions of the breast may at times simulate cancer. Because of chemo- and antibiotic therapy, breast abscess is no longer a common disease, but these agents may so change the character of the inflammatory reaction that differential diagnosis is difficult. Exploration of such a lesion should include a biopsy of the abscess wall even when pus has been found.

## Tuberculosis

Tuberculosis of the breast is found in patients with tuberculosis elsewhere in the body and, until sinus form, the lesion may be confused with cancer.

## Plasma-Cell Mastitis

Plasma-cell mastitis may mimic breast cancer. In the acute phase it resembles an infection with pain, tenderness, and local redness, with or without a discharge from the nipple. Later the lesion becomes firm, nontender, and often adherent to the skin, and the axillary lymph nodes may be enlarged.

## Traumatic Fat Necrosis

Traumatic fat necrosis occurring usually in full or pendulous breasts of times cannot be differentiated from breast cancer. In about one half of patients with this condition a history of trauma is not obtained. The local lesion is hard, adherent to the surrounding breast tissue, and usually adherent to the skin, making a clinical distinction from cancer impossible. Following excision, both the surgeon and the patient are pleasantly surprised.

## Chronic Cystic Mastitis

Chronic cystic mastitis is most commonly found in patients between 25 and 45 years of age. While the relationship of this lesion to cancer is not clearly defined, its presence does not exclude the possibility of cancer. The manifestations vary from a shottiness in one or both breasts—often diffuse, but commonly more marked or limited to the upper outer quadrants—to

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the finding of a firm, isolated nodule fixed to breast tissue and palpable axillary lymph nodes. Inflammation or rupture of cysts with resulting inflammation produces a lesion that may be firm, fixed to breast tissue, and adherent to the skin. It is in this disease that the term "dominant lump" has become important. The only question of this term has to do with the size of such a lump. If lumps no larger than a few millimeters are included then the term may be safely used. Area excision of such lesions is necessary for accurate diagnosis, and continued regular follow-up examinations of these patients must be carried out.

### Fibroadenoma

The fibroadenoma is the most common benign tumor of the breast. It is seen usually in younger women, is most often single but may be multiple in one or both breasts. Called the "slipper" tumor because of its extreme mobility within breast tissue on physical examination, it is seldom confused with cancer. Its importance lies chiefly in the fact that breast adenofibrosarcoma may arise from such a tumor left undisturbed or after incomplete removal.

### Intraductal Papilloma

Intraductal papilloma usually produces a discharge from the nipple that is often bloody. Chronic cystic mastitis and breast cancer may also produce discharge from the nipple, so that duct discharge alone is

not diagnostic. The patient may have discovered a small mass under or adjacent to the areola that, when compressed, results in nipple discharge. Careful physical examination usually discloses the tumor and pressure may be painful. Special methods of examination, such as staining of the secretion for cells, transillumination, or mammography, are seldom indicated. Excision of the involved duct, with its breast quadrant, followed by careful histological study of the tissue is the only means of establishing the diagnosis. Other benign tumors may occur in the breast as sebaceous cysts and lipomas, but these do not differ from similar lesions elsewhere.

### Male Breast

The male breast, a rudimentary structure, is subject to all of the many lesions found in the female breast. Since carcinoma of the male breast is a highly malignant lesion, excision of the entire male breast, with careful histological study, is indicated if benign disease is suspected. The nipple may be preserved if the lesion is benign.

### Conclusion

The family physician and the surgeon accept grave responsibility in caring for patients with suspected benign breast disease. The differential diagnosis of benign breast disease is of great clinical interest. Excision of surgically benign breast lesions with careful histological study is necessary to determine the final diagnosis.

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Keratosis senilis is a precancerous lesion, differing only in degree from squamous-cell carcinoma or Bowen's disease.

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# NEVI



Blue (Jadassohn-Tièche) nevus on dorsum of hand, a typical site.



Junctional nevus. Nevi in childhood are almost always junctional. Active cell changes persist into adulthood in 70 per cent of junctional nevi on the feet. Hence all nevi on the feet should be excised.



Compound nevus on foot. Dermal nevus compounded with junctional changes. Nevus is elevated, with brown background, and peppered with bluish-black areas.

Regional Distribution of Malignant Melanoma. Areas More Darkly Shaded Show Higher Incidence.

HEAD & NECK  
28.9%

PRIMARY  
SITE NOT  
DETERMINED  
2.6%

TRUNK  
23.6%

UPPER  
EXTREMITIES  
10.9%

GENITALIA  
8%

ANORECTAL  
1.5%

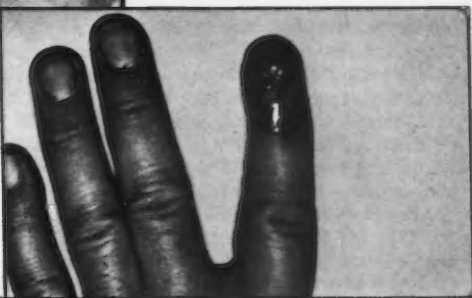
LOWER  
EXTREMITIES  
29.6%

Pack, G. T.; Lenson, N., and Gerber, D. M.: Regional distribution of moles and melanomas. *A. M. A. Arch. Surg.* 65: 862-870, 1952.

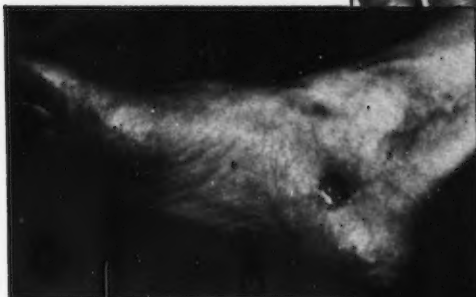
# MELANOMAS



Typical melanoma, present as long as patient could remember. No evidence of regional node metastases, seven years after wide excision and skin graft.

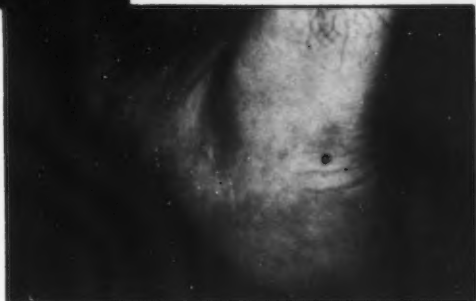


Subungual melanoma. Typical granulomatous pannus over the nail bed with small pigmented areas of melanoma.



Nonpigmented melanoma, which, on previous biopsy, had been felt to be anaplastic skin cancer.

Early malignant melanoma. Only a four months' history in a man of 30 years. Excised as a junctional nevus but, histologically, true malignant melanoma.



# Leukoplakia Buccalis

*Charles R. Rein, M.D., and J. John Goodman, M.D.*

In these days of preventive medicine and cancer-detection clinics, it is quite natural that extra emphasis has been placed on the precancerous lesions. Also, the present hue and cry of tobacco as a major factor in the etiology of lung cancer has focused the attention of the lay populace and medical authorities alike<sup>1,2</sup> on the detrimental effects of smoking. Smoking also plays an important role in producing leukoplakia of the buccal mucosa, a precancerous lesion,<sup>9</sup> with which this report mainly concerns itself. There is, therefore, a suggestive parallelism between leukoplakia of the oral cavity and cancer of the lung. It is felt that the continuous exposure to chronic irritation produced by the products of combustion and heat of smoking is a definite causative factor in both the production of leukoplakia buccalis and pulmonary cancer. Both leukoplakia and cancer of the lung occur predominantly in males and it is thought by many that the male species has an inherent susceptibility. However, Graham feels that the increased incidence of pulmonary carcinoma in males is due to the fact that fewer women of cancer age smoke and that it is chiefly the teenagers and young women who are the heavy female smokers. He is of the opinion that a statistical study in another ten to fifteen years will reveal a more proportionate division. Evidence continues to accumulate on the role of smoking in cancer of the lung. For example, in Iceland, where cigarette consumption is markedly less than in the United States, primary cancer of the lung is still a rarity.<sup>1</sup>

The main two types of cancer of the lung are the epidermoid or squamous type and the adenomatous type. It is speculated that the adenomatous type arises from fetal bronchial buds and the squa-

mous-cell type is caused by a metaplasia of the adult bronchial epithelium owing to the action of carcinogenic agents, such as smoking. It is of special significance that only the squamous-cell type of cancer of the lung has shown such a marked increase in the past decade. The initial metaplasia of the bronchial epithelium and the leukoplakic lesion of the buccal mucosa can be produced by similar carcinogenic irritants with the ultimate progression of both lesions into the squamous-cell type of cancer. Unfortunately, in cancer of the lung, the early histological changes are not visible, the patient is completely asymptomatic; and when symptoms, such as cough, weight loss, pain and hemoptysis, finally do appear, progression to the frank squamous-cell pathology has already occurred.

The term "leukoplakia"<sup>12</sup> etymologically is derived from the Greek, leukos, white—and plax, plaque. The condition was first described by Bazin and others as a type of lingual psoriasis, but it was Schwimmer, in 1877, who differentiated it from psoriasis and described it under its present name.

Leukoplakia of the oral cavity, otherwise known as leukokeratosis, leukoplakia buccalis, or smoker's patch, is a relatively common condition. When first seen, it appears on the buccal mucosa as a bluish-white or bluish-red patch that is sensitive to chemical irritation and to hot and cold foods. Older lesions take on a dull grayish hue and are slightly raised, indurated, nontender, and somewhat rough to the touch. Upon removal of the grayish patch, bleeding will result. When these lesions show evidence of cracking, fissuring,

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and ulceration, malignant transformation must be suspected.

Hazen and Eichenlaub<sup>6</sup> believe that leukoplakia or leukokeratosis may be considered somewhat analogous to senile keratosis, in that the former is a defense reaction to irritation in the mouth, while the latter is a similar reaction resulting from actinic or other irritations to the skin. Thus, senile keratosis represents a precancerous lesion of the skin, while leukoplakia buccalis represents a precancerous lesion of the oral cavity. Histologically, they also represent the same process. Lain feels that light-complexioned individuals are definitely more predisposed to the formation of both senile keratoses and leukoplakia. Fox agrees with this premise, having previously stated in 1925 that leukoplakia is very rare in the Negroes. It would seem that pigmented skins offer more protection against irritant agents and subsequent hyperkeratinization of epithelial tissue.

### Etiology

In considering the cause of leukoplakia, the essential factor appears to be an exposure to chronic irritation, whether it be traumatic, thermal, physiochemical, or electrogalvanic with smoking as the most important agent. McCarthy feels that the pipe is the most irritating form and noted a correlation in smoking habits and the resultant lesions, in that one-sided smokers tend to produce a unilateral lesion. Nonsmokers may also develop leukoplakia buccalis as a result of malocclusion, faulty dentures, and sharp tooth edges. Several decades ago, syphilis was thought to be a definite cause of leukoplakia, but further studies<sup>2</sup> indicate that, although it is not a major factor, it may predispose an individual to the development of leukoplakia of the tongue. Lain feels that the saliva of the mouth, acting as an electrolytic solution, sets up electrogalvanic currents between dissimilar metals, such as are found in dentures, thereby producing burning and stinging of the buccal mucosa with subsequent

leukoplakic formation. Hazel et al. are of the opinion, however, that the electrogalvanic currents in themselves are too weak to produce a significant damage to the buccal mucosa but noted in spectrographic studies on biopsies of leukoplakia that one specimen contained an abnormal concentration of cadmium, while others showed abnormally high concentrations of silver. They felt that metallic ions from dental restorations were being deposited in the buccal mucosa. They also are of the opinion that altered reactivity to metallic ions from dental restorations may explain many of the subjective and objective symptoms of the so-called electrogalvanic lesions and might be a possible etiological factor in leukoplakia. Another interesting agent of chronic irritation is the chewing of the betel-nut quid, common in parts of India.<sup>10</sup> The betel-nut quid is usually made up of lime, tobacco, betel nut, and black catechu, a flavoring agent. The exact ingredients of the betel-nut quid vary with the area and, in some parts of India, where the ingredients are more irritating than in others, there is a higher incidence of leukoplakia and oral cancer. Other minor types of chronic irritation include the exposure to hot and spicy foods, habitual biting of the cheeks, and the ingestion of certain exotic foods that may liberate irritating chemicals. Also, it has been said that avitaminosis or anemia may be predisposing factors.

### Diagnosis

The differential diagnosis of leukoplakia buccalis includes syphilis, lichen planus, thrush, lupus erythematosus, and exudative processes in the mouth. Syphilis should be ruled out by investigating the serology and other concomitant signs. Lichen planus, at times, can be exceedingly difficult to differentiate, and the histological picture unfortunately may also be confusing. Clinically, in lichen planus one usually finds dendritic, whitish, symmetrical papular lesions on the buccal mucosa of both cheeks. If lichen-planus lesions are noted elsewhere on the skin,

the problem is greatly simplified. Mycological studies should be performed in differentiating cases of thrush. On occasions, one may see an involvement of the oral cavity by lupus-erythematosus lesions, but they are usually painful and frequently show signs of ulceration. Here again, the presence of characteristic cutaneous lesions is helpful in establishing the diagnosis. Exudative lesions are characterized by the fact that the exudative material can be readily removed, leaving a raw surface.

### Therapy

The most important therapeutic approach is the removal of the cause, if feasible. If smoking is the agent, then it must be stopped; if it be an ill-fitting denture, malocclusion, or rough teeth edges, then the proper dental work should be initiated at once. If the agent causing the chronic irritation can be removed, many leukoplakic lesions will tend to resolve. Thus, many lesions of leukoplakia resulting from tobacco have cleared up on the cessation of smoking.<sup>8</sup> Proper oral hygiene should be instituted in any case of leukoplakia. Each patient should be considered individually and observed periodically for carcinomatous changes, since the majority of lesions require no specific treatment. The onset of cracking, ulceration, and fissuring, however, heralds

the beginning of cancer and definite steps should be taken. The literature abounds in the usage of many modalities such as roentgen rays, radium, electrolysis, carbon dioxide snow, surgery, caustics, electrodesiccation, and electrocoagulation. Radium or roentgen-ray therapy is not to be advised, since it replaces the involved area with devitalized tissue. McCarthy opposes the use of caustics, since he feels they might stimulate malignant changes. Surgery, electrodesiccation, and electrocoagulation are the preferred methods of treatment.

### Summary

1. Leukoplakia of the oral cavity is essentially produced by factors causing chronic irritation such as smoking, malocclusion, ill-fitting dentures, rough tooth edges, betel-nut chewing, and the like. Smoking in leukoplakia, as in cancer of the lung, is considered a major cause.

2. Good oral hygiene should be maintained and chronic irritating factors eliminated.

3. Each case of leukoplakia should be considered individually. Signs of beginning malignant changes are fissuring, ulceration, and cracking and require definitive treatment. Preferred specific methods of treatment include surgical excision or complete destruction by electrodesiccation or electrocoagulation.

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# CANCER CLINICS



## WOHL HOSPITAL

Washington University School of Medicine  
St. Louis, Missouri

## Washington University Tumor Clinic

Conducted by *Charles Eckert, M.D., and Lauren V. Ackerman, M.D.,*  
January 11, 1954

### Case 1. Osteochondroma of the Iliac Bone

DR. BRADLEY: A 23-year-old white woman entered the hospital with a three years' history of a mass on the right iliac crest. The growth had been fairly constant, and at no time had there been any history of pain. Remainder of the history was negative. On admission to the hospital, physical examination revealed a 4×8-cm. mass that was hard, fixed, and slightly tender. It was positioned at the right anterior iliac spine. The laboratory findings were within normal limits. Roentgenograms had been made on the patient elsewhere.

DR. SEAMAN: A roentgenogram of the pelvis revealed a pedunculated bony outgrowth arising from the region of the anterior superior iliac spine (Fig. 1). It has the type of trabeculation found in normal bone and resembles the classical appearance of an osteochondroma.

DR. ECKERT: Dr. Ramsey, if given such a lesion clinically and by roentgenogram, what would you recommend be done?

DR. RAMSEY: I feel that in the absence of similar bone lesions, which would be carefully looked for, excisional biopsy should be done in a small lesion, such as this. The roentgen-ray appearance is very typical for osteochondroma.



FIGURE 1. Roentgenogram to demonstrate well-defined osteochondroma of the right iliac bone. (W. U. 54-532.)

DR. ECKERT: What is the life history of this tumor if it is not removed?

DR. RAMSEY: You would expect it to enlarge gradually over a period of years causing an increase of symptoms, and there would always be a possibility of malignant change.

DR. ECKERT: Is there any possibility that other diagnoses must be considered or is this osteochondroma?

DR. RAMSEY: I don't believe so. Malignant change could be found even in a lesion of this size.

DR. ECKERT: How often does malignant change complicate the course of an osteochondroma?

DR. ACKERMAN: I would say that chondrosarcoma can arise from a benign cartilaginous growth. There is little danger of such a transformation in the small bones of the hands where cartilaginous growths are common, and there is very little chance of malignant change taking place in the small bones of the feet. The

greatest chance of such changes taking place in cartilaginous tumors is within the long bones and in cartilaginous tumors arising from the bones of the pelvis. The exact question of the frequency of malignant change in a group of osteochondromas, of course, I really cannot answer except that the relative frequency would be low. The peripheral chondrosarcomas often arise in the pre-existing osteochondromas from their cartilaginous cap, and those changes are usually seen after the age of puberty when there may be an increase of growth with increase of size.

DR. SEAMAN: If an accessible osteochondroma is not causing the patient any trouble, should it generally be biopsied or excised?

DR. RAMSEY: I think such osteochondromas should be excised if found during the course of roentgen-ray examination. The exception is the patient with multiple lesions, for it is not feasible to remove them all. If one of these osteochondromas becomes more active and produces symptoms, then it must be removed. But, given a solitary lesion like this without symptoms, its location increases the possibility of malignant changes taking place within it.

DR. SEAMAN: My impression is that we see osteochondromas quite frequently during the course of routine roentgen-ray examinations.

DR. ACKERMAN: But by the time they get to the orthopedic surgeons, I am sure they are ones that are giving symptoms because of pressure or they are in a site, such as this one, where somebody finds it.

DR. SEAMAN: This is true, but what about small ones unknown to the patient?

DR. ECKERT: Let's not make this a question of incisional versus excisional biopsy in the case of this lesion. It certainly seems as if the best way to approach it would be to remove the entire lesion.

DR. ACKERMAN: In the long bones, that is usually the procedure of choice except in the case of large lesions.

DR. RAMSEY: Do I understand you to say that, by and large, these malignant lesions started as malignant lesions?

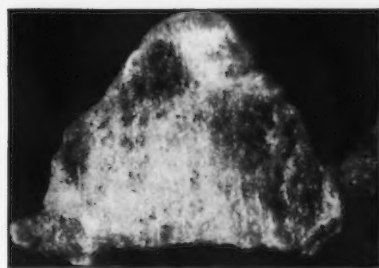


FIGURE 2. Gross photograph to demonstrate cartilaginous cap of the osteochondroma seen in Fig. 1. (W. U. 53-6972.)

DR. ACKERMAN: No, I do not believe I said that exactly. I think that it may be very difficult to say in a given case whether the lesion has always been malignant. You may have a history of an osteochondroma pre-existing over a long period, which suddenly shows increased growth potential. When you take it off, and it is malignant, you assume that it might have been an osteochondroma in the past that became malignant at some time.

DR. RAMSEY: The differentiation can always be made only after an operation?

DR. ACKERMAN: Well, the differentiation at times may be difficult in all aspects. The evidence of malignancy is dependent upon (1) the site of the lesion, (2) the history of the lesion, and (3) the gross picture. Of course, an obvious lesion would not give you any trouble because it would be growing out of the soft tissue, but, in an early one, the most important fact is the thickness of the cartilaginous cap. In a review of our cases here we found, almost without exception, that, if the lesion was malignant, the cartilaginous cap usually measured 3 or more cm. and often the tumor was large. So, if you had a tumor in this location in this age group with a history of recent, rapid growth, which measured 8 cm. or more, and it had a thick cartilaginous cap when you took it out, this would imply that it was probably malignant. Microscopically there are also alterations that have to be taken into consideration.



FIGURE 3. Cartilaginous cap of osteochondroma. Note uniformity of cartilaginous cells and nuclei. (W. U. 54-283.) ( $\times 120$ .)

DR. ECKERT: Has this lesion been removed?

DR. ACKERMAN: Yes; and the cartilaginous cap of this lesion was relatively thin.

DR. ECKERT: Do you know how much it measured?

DR. ACKERMAN: It measured 0.4 cm. or so. We took sections through the cartilaginous cap—here is the osteochondroma and here is the cap (Fig. 2). Now the cartilaginous cap of an osteochondroma will vary in thickness and it will be covered by a thin layer of perichondrium. We usually pay attention to the growing edge of this lesion and look for alterations in the cartilage cells. You will see that this is a very thin cartilaginous cap. These are adult cartilage cells, and they show no aberrations that we think would indicate that they are malignant (Fig. 3). Those aberrations include mul-

tipule nuclei and atypical nuclei. Those changes in the past were not too well recognized until Jaffe emphasized their importance.

DR. ECKERT: Are there any more questions? Next case please.

## **Case 2. Benign Adenomatous Polyp of the Sigmoid Colon**

DR. BRADLEY: This 44-year-old white woman entered the hospital in December, 1951. Her story was briefly that she had experienced transient right lower-quadrant pains with severe cramping; this was not repeated. Shortly before admission she had air contrast studies done in Birmingham, Alabama, that were said to show polyps of the sigmoid colon and upper descending colon. Those films are not available at the present time. Barium studies repeated at Barnes Hospital did not show these polyps. According to the written report, on December 14, 1951, the patient was explored. The findings were that she had a polyp of the sigmoid colon. Exploration of the upper descending colon did not reveal any polyps.

DR. ECKERT: And no other polyps could be palpated in the remainder of the colon.

DR. RAMSEY: Was a sigmoidoscope used in this operation?

DR. ECKERT: Not in this case.

DR. RAMSEY: Where was the polyp removed?

DR. ECKERT: Sigmoid colon, mid-sigmoid.

DR. BRADLEY: The patient has had subsequent check-ups via contrast enemas. Roentgenograms were reported as negative until December, 1953, at which time air-contrast studies done here revealed a questionable polyp in the sigmoid colon near the site of the previous polyp. There is also a statement that there is a polyp in the upper descending colon.

DR. SEAMAN: That is not quite right. The polyps were found in 1952. She had a series of five barium enemas in the fall of 1951. The examination done in December, 1951, was reported as negative.

In retrospect there is an area that is very suspicious of a polyp. There is one filling defect that is not constant in the mid-sigmoid. Whether this remains the same as this, it is hard to say, for it could represent the same thing as the polyps in the 1951 examination. The one suspicious shadow is just above the rectum in the sigmoid colon. The next examination was done in June, 1952, and in the film there is a small defect a little less than 1 cm. in diameter, which corresponds roughly to the site in which the suspicious area was seen.

DR. ACKERMAN: Could this be fecal material?

DR. SEAMAN: It can always be fecal material. You can never on the basis of any one examination for a polyp of the sigmoid colon be certain that it is a polyp. Actually, I think the working rule in any polyp of the colon should be that it should always be verified by at least one additional examination. One striking example of that occurred several years ago when a patient had two shadows on an air-contrast enema that looked like polyps. One was accessible from below and a polyp was subsequently seen on sigmoidoscopy and removed. The second shadow was explored from above and nothing was found, yet radiographically they looked identical. Never on the basis of a single examination can one be absolutely sure that the shadow is not an air bubble or a loose piece of fecal material. On this examination, as well as that, however, there are several areas in the descending colon that are fairly smooth, round, and small, measuring 3 to 4 mm. in diameter, that could represent polyps; at the time we thought they were more likely air bubbles, because they could not be demonstrated on any other films. So this examination, in June, 1952, suggests a polyp of the proximal sigmoid and other small radio-lucent defects in both the distal transverse colon and the descending colon, probably air bubbles. That cannot definitely exclude the possibility of their being small polyps. The next study was done in 1953.

DR. ECKERT: I can give the symptoms,



if Dr. Bradley cannot. She had practically no symptoms with the exception of occasionally noting small amounts of blood in her stools.

DR. SEAMAN: On examination of October, 1952, radiolucent areas were again seen vaguely in the filled colon about in the same position as seen in the previous examination; they were also suggested on the air-contrast enema. Here again we have some filling defects that are quite irregular and look more like fecal contents. On a detailed film we have a very faint suggestion of radiolucent filling defects in the sigmoid colon. The next examination was in July, 1953. These are all postoperative. Of course, this examination again showed radiolucent filling defects, slightly less than 1 cm., in the same position, roughly proximal to the sigmoid colon.

DR. ECKERT: I think these were higher than the original polyp.

DR. SEAMAN: This is approximately the site, however, where there was a suspicious shadow on the original postoperative films, but you found nothing at that time. Since July, 1953, the most recent examination (done in December, 1953) again showed the same radiolucent defect in approximately the same portion of the descending colon. On the air-contrast film, again, similar small defects in the descending colon were seen, which you may recall were present on one or two of the previous films and which look a little like air bubbles. On the other hand, it was suggested that several of them might be in the same place, both in the proximal transverse colon and the descending colon. With defects this small and in an organ as collapsible and elastic as the colon, it is difficult to be sure whether they are exactly in the same place. Only if they correlate and maintain a constancy in position can we be sure that they actually represent pathology and are not an air bubble or a piece of fecal material. However, because of these two in the upper descending colon, which can be seen a little bit better on spot films, a question was raised whether this was not only a



FIGURE 4. Roentgenogram of bowel by air contrast showing how well a pedunculated polyp can be demonstrated. (W.U. 52-827.)

polyp here, but whether there might not be multiple small polyps in the descending and perhaps a distant portion of the transverse colon. I think it is fairly definitely demonstrated that there is a persistent filling defect in the proximal sigmoid and possibly small polyps remain in the colon. In the condition of multiple polyposis we have made the mistake in the past of seeing small round shadows that look like air bubbles but that turn out to be multiple, small, smooth polyps in the colon. It can be a very difficult radiographic diagnosis (Fig. 4).

DR. ECKERT: First of all, we know this patient has no familial history of polyps. We have multiple films prior to her first operation that showed a defect in the same position. We felt reasonably certain that a polyp was present, and one was found at the position at which it had been predicted. However, attempts to demonstrate other polyps were unsuccessful, although the bowel was opened at other points. In the follow-up examination of the patient she complained of blood in her stools, and these films that Dr. Seaman has gone through were obtained because



FIGURE 5. Benign adenomatous polyp with well-defined stalk and uniform glandular pattern. (W. U. 54-284.) (Low power.)

of the fact that polyps should be considered as precancerous lesions. Given a polyp of relatively small size, it is difficult to reoperate on patients on multiple occasions for such lesions, and one must be as certain as possible before recommending re-exploration. We have about reached the point of being certain in this case, and this patient is scheduled to return to the hospital in February for re-exploration and removal of polyps.

DR. ACKERMAN: Now at the time of the exploration is there any method of verifying the presence or absence of polyps in the other portions of the large bowel?

DR. ECKERT: Many methods are available. The most favored of these is the performance of multiple colotomies with the introduction of a sigmoidoscope, allowing the actual visualization of every portion of the surface area. This can be

done through about three openings, and you can visualize practically all of the mucosa of the large bowel in that way. This is the most certain way of demonstrating polyps. Preparation of the bowel is, of course, necessary but we have not had much difficulty with that.

DR. ACKERMAN: If you have a single well-defined polyp in the upper sigmoid and you go in after it and the patient is, say, age 30, is it justified or indicated that you do this procedure or will you be content with palpation or just looking in the immediate area?

DR. ECKERT: Well, obviously there was a little divergence in what was done in this case and what I have been saying. This is due really to some change in my own attitude. At the time of the original operation this was not done, and I feel that very likely we overlooked the polyp because it was not done. On the other hand, at this time we do it as a measure routinely in the exploration for polyps.

DR. ACKERMAN: Another point that bothers me, however, in the follow-up of this patient who has had one polyp and whom you are committed to follow because of chances of other polyps: the question is always raised with any one to whom you talk to as to how often the patient should have stool examinations for occult blood. How often should you do sigmoidoscopies and how often should you do barium enemas? If you do barium enemas very often this will run up into a little money. Is it justified?

DR. ECKERT: Well, I think it is certainly justified when you have occult blood in the stool or any symptoms suggesting additional polyps, as in this case. We have performed sigmoidoscopic examinations and barium studies of the bowel at six-month intervals since the time of operation. However, in patients in whom there are no signs of occult blood, I would certainly not believe that re-examination is necessary more often than once a year, and then probably for only a limited period of time, so long as they continue to be asymptomatic and have no occult blood in the stool.

DR. SEAMAN: I would think that examination of the stool would be a better way and certainly a less expensive way to follow this type of patient.

DR. ECKERT: Well, it is a sort of screening procedure. If you are satisfied that sufficient specimens have been obtained to allow you to draw conclusions from a single stool specimen, it can be very misleading.

DR. ACKERMAN: We have a section of a polyp removed the first time (Fig. 5). One of the most prevalent types of specimens that we receive are polyps of the large bowel, and they cause us a great deal of mental anguish. Of course, if you have a polyp that is obviously malignant, or obviously benign, that is not so difficult. This particular one has a well-defined stalk without any invasion of the stalk and epithelium that is not completely benign—the individual glands show some tendency toward stratification of cells and loss of nuclear polarity. This we can designate by some phrase, such as "focal atypical changes are present," which just indicates that we do not know what is going on or what is going to happen in the future. Certainly if you know that a stalk is present and there is no real evidence of cancer, then you can say that the chance of cure is higher with this particular polyp.

DR. SEAMAN: Where do cancerous changes take place in polyps?

DR. ACKERMAN: Cancerous alterations can occur at any point in the polyp, whether it is in the top or the bottom.

DR. ELMAN: I would say that I have changed my attitude along with Dr. Eckert. In the last three cases that I removed at exploratory laparotomy, I have used the proctoscope. I think that it gives you a better feeling that there are no further polyps. You can go all the way down to the opening where the polyp was removed. This I think is better than palpation from the outside.

DR. ECKERT: Well, palpation from the outside, even with a thin person, would give you a good margin of error. With an obese person it would be almost impos-

sible because it is extremely difficult to tell a polyp from other bits of fat, etc.

DR. ELMAN: Dr. Eckert, do we have any statistical information or follow-ups on people who have had a single polyp.

DR. ACKERMAN: Well, there are many articles written on the subject. If you have a patient who has a polyp or a group of patients with polyps, they have a much greater chance of developing cancer than another group of the population. If you follow those patients over a period of time, a fair number of them will develop cancer of other areas, usually not in the same areas of the colon.

DR. ELMAN: Now there is another point I should like to ask. It is a lot different, as I see it, in examination of the bowel radiographically if you just fill the bowel up with barium or if you do air contrasts. It seems to me from the standpoint of identifying small lesions, if you have constant defects, there can be a small polyp. If you have good examinations by good radiologists like Dr. Seaman, how often do you think you are going to pick up something? In other words have you picked up any polyps at the time of operation that the radiologist has missed? I have picked up polyps on proctoscopic examination from below in cases that have repeatedly had negative barium-enema and contrast studies.

DR. ECKERT: I should like to emphasize the fact that the rectum is not to be examined by either filling it with barium or air contrast, because it is an extremely difficult place to visualize.

DR. ELMAN: I think this also emphasizes the fact that one should use as many methods of examination as are feasible rather than rely on one single method of examination. Dr. Smith told me at the Mayo Clinic that he had this discussion with a radiologist and he has records of ten cases in which he found a polyp of the sigmoid by visualization.

DR. SEAMAN: Well, I think it is still possible to find it by roentgenography but I also think that every patient, when possible, should have a sigmoidoscopic examination because the rectum and the recto-

sigmoid area is difficult to examine radiographically.

DR. ECKERT: I think the radiologists are constantly surprised at the number of patients whom they see because of questions of this sort in whom preliminary rectal examination and proctoscopic examinations have not been carried out. At least they have indicated that to me.

DR. SEAMAN: I think that is true. We get patients sent up for barium enemas in whom digital examinations have not been done.

DR. ECKERT: Needless to say, this is not the ideal way to practice proctology. Dr. Ackerman, would you care to say anything about predisposition of retention polyps and benign adenomatous polyps toward the development of malignant change?

DR. ACKERMAN: I would say that there is a great body of evidence that supports the concept that there is probably a much higher percentage than we think of adenocarcinoma of the large bowel arising from pre-existing adenomas. In other words, we know that, in the first place, the distribution of cancer and the distribution of adenomas are similar; second, that we frequently find cancer in all stages of development in a surgical specimen; and, thirdly, that it is not rare to find a polyp with half of it cancerous and half of it benign. So I would say that the adenoma of the large bowel is really an excellent example of tissue that stands a good chance of becoming cancerous and that there is a real indication for its removal.

DR. ECKERT: Are there any further questions?

### **Case 3. Intraductal Papilloma of the Breast**

DR. BRADLEY: The last case is that of a 63-year-old colored woman who entered the hospital with the complaint that for three months prior to admission she has noticed a brownish stain on her left brassière cup. She had not palpated her breast or noted any pain at any time. In addition this patient had experienced low-

back ache for a short time prior to admission. She was seen first in the Surgical Clinic where physical examination of the breast revealed an ill-defined mass in the upper inner quadrant of the left areola. On pressure, a bloody discharge could be produced. This was repeated several times prior to operation. Roentgenograms were taken of the chest and also of the dorsal spine.

DR. SEAMAN: Films of the dorsal spine taken in September, 1953, were read as a compression fracture of the ninth dorsal vertebra. Actually there is a minimal loss of vertical measurement despite the irregularities of the cortical plate. I would have to call it a questionable fracture, either of traumatic or neoplastic origin, even though it is difficult, to be sure, to distinguish those two types. The chest films show cardiac enlargement, which is minimal. The aorta and lung fields are essentially clear, showing no metastatic involvement.

DR. ECKERT: In this particular case both a palpable mass and a bloody discharge from the nipple existed. However, it should be realized that it is not infrequent to see a bloody discharge from a papilloma in a major duct, without a mass. The problem is considerably greater, however, when no mass can be palpated. Under these circumstances, we attempt to localize the duct from which the discharge is occurring. This is best done by making gentle pressure on all parts of the areola and the breast tissue just peripheral to the areola and milking toward the nipple in an attempt to localize the area from which the discharge is coming. Under these circumstances, we feel that incision in that area has a good possibility of demonstrating the pathological change that is producing a bloody discharge.

DR. ACKERMAN: I did not hear the size of this palpable mass.

DR. BRADLEY: No size was given.

DR. ACKERMAN: I asked how big it was because microscopically it does not look very big. There are some dilated ducts and it is possible that what was being felt was

an area in which the ducts were thickened. There was a small intraductal papilloma present, and there was no evidence of any malignant change in this intraductal papilloma (Fig. 6). It has uniform cells well supported by delicate connective tissue. The stalks are usually highly vascularized and, because of the vascularity and cellularity, bleeding is bound to be common.

DR. ECKERT: The greatest question with regard to these clinical findings is how frequently a cancer exists and gives rise to a bloody discharge when no palpable mass is present. The information from the literature is somewhat conflicting. Haagensen and Stout reviewed their material and, to my knowledge, have no case of cancer in the absence of a palpable mass with a bloody discharge. Is that correct? (Table I.)

DR. ACKERMAN: I believe so. There is another series from Johns Hopkins by Lewis, reported in the Journal of the American Medical Association, in which there was a fairly high frequency of bleeding with cancer. When you exclude all the cases in which there was a real palpable mass or Paget's disease, there were only a small number of patients with cancer. If you take a group of 100 known cancers, bleeding as a symptom does not exist in more than 5 per cent of the group.

TABLE I

**Follow-up of Seventy-six Patients with Intraductal Papilloma of the Breast Treated by Local Excision—Presbyterian Hospital, 1916–1941\***

Site	Treat. local excis.	Recurr. pap.		Devel. ca.	% follow-up
		Less than 5 yr.	More than 5 yr.		
Centr.	56	2	0	0	94.6
Periph.	20	0	1	0	95.0
All	76	2	1	0	94.7

\*Compiled from Haagensen, C. D.; Stout, A. P., and Phillips, J. S.: The papillary neoplasms of the breast. I. Benign intraductal papilloma. *Ann. Surg.* 133: 18-36, 1951.

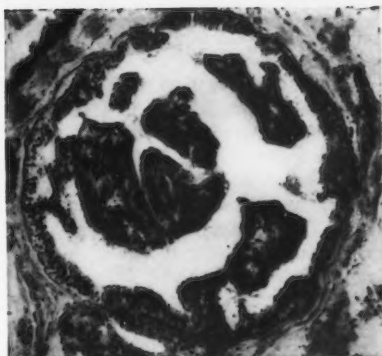


FIGURE 6. Benign intraductal papilloma confined to the duct. (W. U. 54-280.) (Low power.)

Finally, from the standpoint of a microscopic pattern of the lesions, I personally have never seen an intraductal papilloma that was becoming cancer, or was half cancer, or in which the patient had had partial removal of an intraductal papilloma and the remaining portion had become cancer. We have seen cancer coexist with an intraductal papilloma but bearing no relation to it. It is of interest that in no instance did Haagensen and Stout get into any trouble in their series of some seventy-six cases in which surgical removal was done.

DR. ELMAN: What is causing the mass?

DR. ACKERMAN: I think just a little thickening of the ducts, but I think it was an indefinite mass probably in this case. What do you think, Dr. Eckert?

DR. ECKERT: I do not see how we can give a really good explanation for a palpable mass here. I think the essential point is this, that if there is no palpable mass you cannot localize the point from which bleeding has occurred. Presumably with intraductal papilloma you are justified in repeated observations over a long period of time rather than in performing a more radical procedure, such as simple mastectomy, which many people have recommended under these circumstances. There have been authors who have listed, as their experience, up to 4 or 5 per cent

of cases in which unsuspected cancer was found under these circumstances. If the percentage is as high as 5 per cent, it might give some support to the advocates of a simple mastectomy. On the other hand, in my personal experience, I have had the opportunity to follow at least five women in whom I could not demonstrate the site of discharge over a period of years. The discharge has ceased and I have never been able to find it. Nothing has happened. This is still over a limited number of years, but I have not felt that a simple mastectomy could be recommended.

DR. SEAMAN: Have you ever tried injection of the ducts with an opaque agent?

DR. ECKERT: We have tried it but have not found it particularly useful. It is extremely difficult actually to inject such ducts. You can probe them with a fine probe but, when you come to inject the ducts themselves, you find you are injecting surrounding breast tissue.

DR. ELMAN: Dr. Seaman, how do you feel about radiography of the breast itself as advocated by Dr. Cohen from Philadelphia?

DR. SEAMAN: Dr. Cohen has published some very pretty pictures but I personally cannot see that it has any place.

STUDENT: Why can you not see which duct the blood is coming from?

DR. ECKERT: Well, actually, anatomically, the arrangement of the ducts on the nipple is quite variable. In certain cases you have major ducts terminating off the

ampulla and then you have perhaps two openings for all of the ducts. In other cases you may have individual openings of the ducts. Now, if you have any type of ampulla formation, it becomes absolutely impossible to say from which duct the bloody discharge is occurring.

DR. ACKERMAN: One other practical point is that, if you have a patient with intraductal papilloma and there is no palpable mass and the surgeon cannot find it, it is not a good idea for a pathologist to do a frozen section because it might be so difficult to interpret that he would make a mistake. The interpretation of these papillary tumors may be difficult even on permanent sections so as a rule we do not do frozen section.

DR. ECKERT: There is also a question in the literature concerning multiple papillomas in major ducts. In some persons' experiences it has been quite common and in others rather uncommon to find multiple papillomas. Certainly multiple papillomas of the smaller ducts within the breast tissue itself are quite common; when you are speaking of intraductal papillomas producing bleeding from the nipple, it means, of course, papilloma occurring in the larger duct and it has been our experience that papillomas of these ducts have been less common.

DR. ACKERMAN: Having removed a single papilloma there is usually no recurrence of symptoms.

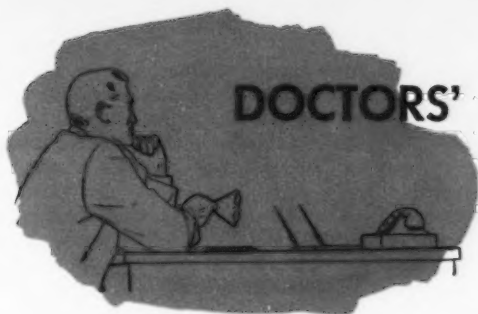
DR. ECKERT: That is correct. Are there any further questions?

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Any program for the prevention of carcinoma of the colon can only be aimed at the known predisposing factors. This means the destruction of polyps wherever found and removal of those colons which are the site of advanced ulcerative colitis or diffuse polyposis. By the destruction of asymptomatic polyps, a great reduction could be made in the number of carcinomas of the colon, particularly those of the rectosigmoid, where most polyps are found . . . we cannot justify failure to sigmoidoscope every patient with a history of rectal bleeding.

McKittrick, L. S., and Wheelock, F. C., Jr.: *Carcinoma of the Colon*. Springfield, Ill. Charles C Thomas, 1954; p. 5.





## DOCTORS' DILEMMAS

**Q** *Do you advise thoracotomy for all solitary lung lesions in which all diagnostic studies are negative?*

**A** Yes—unless a patient has roentgen-ray evidence of an unchanging lung lesion of five or more years' duration or a history of previous tuberculosis resulting in a calcified or fibrotic lung lesion whose evolution is that usually seen following active tuberculosis. Unless such evidence of chronicity is available, the risk of thoracotomy is far less than the risk of "watchful waiting" in a persistent solitary lung lesion, whether or not all diagnostic studies are negative.

**Q** *Recent medical literature indicates a lack of uniformity in both the concept and management of carcinoma in situ. I have under my care a 28-year-old gravida II, para II, who was delivered spontaneously of a normal male infant twelve weeks ago. In the course of the recent pregnancy a cervical smear, done at thirty weeks during a period of minimal spotting, was interpreted as class III and a biopsy of four quadrants of the cervix, which included a minute ulcerated area, was interpreted by two pathologists as carcinoma in situ. The pregnancy was allowed to continue and at the time of delivery the biopsy areas had apparently healed. A repeat cervical smear at that time was interpreted as class II. At five weeks postpartum the cervical smear was interpreted as class I. A four quadrant*

*biopsy done at the same time was viewed by the same two pathologists and interpreted as normal cervical tissue. Your opinion as to further handling of this patient would be welcomed.*

**A** The wide variations that exist in the management of carcinoma in situ of the cervix is recognized by almost every author in current gynecological literature. A little more than a year ago C. H. Davis conducted a poll among members of two leading gynecological groups and, although difference in opinion was expressed, the consensus was that carcinoma in situ was a preinvasive stage of genuine cervical cancer. On the question of whether or not spontaneous regression of cancer in situ occurs, there was less uniformity of opinion but more than twice as many gynecologists felt that spontaneous regression did NOT occur than believed it could happen.

It is to be remembered that in such cases as the one described here the apparent "regression" may be due to the complete excision of the lesion at the time of the biopsy at thirty weeks. This would explain the downgrading of subsequent cytology and the negative biopsy at five weeks postpartum.

From the composite experience of recent workers in the field, it would seem that a safe and conservative approach to this case would consist in repeat cervical smears monthly for three months, with extension of the interval between exam-

inations to three and then six months. In the event of any cytological interpretation other than normal, a "cold knife" circular biopsy should supply the pathologist with adequate material for careful review to determine the presence or absence of residual disease.

Although a total hysterectomy is the treatment employed by many in the presence of a firm diagnosis of carcinoma in situ of the cervix, the lack of evidence of postpartum disease and the age of this patient would favor the more conservative treatment, with the understanding that intelligent follow-up would be maintained.

**Q** What means are used to combat the toxic effects of nitrogen mustard?

**A** Following the rapid intravenous administration of nitrogen mustard, the intravenous administration of 0.25 to 0.5 gm. of sodium amytal has been effective in minimizing some of the distressing

nausea, vomiting, and diarrhea that may follow use of this preparation. The administration of ACTH or cortisone two to three days prior to use of nitrogen mustard has been reported to lessen the frequency and intensity of gastrointestinal symptoms seen in the majority of patients so treated. There is little evidence that any form of therapy can alter the serious bone-marrow depression that affects a few patients given nitrogen mustard.

**Q** If an elderly patient is discovered on routine examination to have chronic myelogenous leukemia, without symptoms or anemia, what treatment would be indicated?

**A** Elderly, asymptomatic patients with chronic myelogenous leukemia should not receive active treatment but should be watched carefully at four-week intervals. Treatment should be instituted promptly should anemia or other significant symptoms appear.

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### Eighty Years Later

I believe it has not yet been published that certain chronic affections of skin of the nipple and areola are very often succeeded by the formation of scirrhus cancer in the mammary gland. I have seen about fifteen cases in which this has happened, and the events were in all of them so similar that one description may suffice . . . in every case which I have been able to watch, cancer of the mammary gland has followed within at the most two years, and usually within one year . . . the sequence of cancer after the chronic skin-disease is so frequent that it may be suspected of being a consequence, and must be always feared, and maybe sometimes almost certainly foretold.—*Sir James Paget.*

*Paget, J.: On disease of the mammary areola preceding cancer of the mammary gland. St. Barth. Hosp. Rep. 10: 87-89, 1874.*

Paget's disease of the nipple is even today occasionally classified erroneously as precancerous. It is *actually cancer*, always associated with intraductal neoplasms and often with axillary metastases even when first seen.

—*Editor.*



# new developments in cancer

## **Lung-Carcinogenesis Theory . . .**

Two men, paired in many respects, share the same lifelong environment. One develops lung cancer. The other doesn't. Why? Steiner (University of Chicago) feels that two important agents may be the difference between a tissue's escape from or capture by cancer: (1) the presence of a natural or extrinsic agent capable of eluting pure and effective carcinogens out of such polyglot substances as soot or tobacco smoke; and (2) small substances that adsorb and inactivate carcinogenic particles. The investigator has run a series of mouse experiments that make this hypothesis worthy of further consideration and study. He suggests that the additive and summation effects of various agents should be borne in mind. In the light of results by Richardson (Memorial Center), Griffin (Stanford) and the Millers (Wisconsin), perhaps one should also consider the possible antagonistic effects of various carcinogens.

## **Caution on Androgens . . .**

Segaloff (Tulane) has issued a note of caution against administering certain water-soluble derivatives of testosterone parenterally. Severe (but not fatal) hemoglobinuria was observed in one patient

treated by continuous intravenous injection of one derivative. Tests showed that rats and dogs could be killed as a result of extensive intravascular hemolysis by giving the drugs subcutaneously or intravenously.

## **Growth Hormone and Red Cells . . .**

Pituitary growth hormone fails to prevent or overcome the anemia associated with removal of the pituitary. However, it does repair an underfunctional marrow. Fruhman, Gerstner, and Gordon (N. Y. U.) have looked into this seeming paradox, and, in rat studies, have reached the conclusion that growth hormone does indeed increase red-cell production. The rise in red cells in the circulatory system may have escaped detection, however, because of a concomitant increase in plasma volume.

## **Two Types of Breast Cancer . . .**

There are two types of breast cancer—one dependent upon estrogen and the other not. Pearson, West, Hollander, and Treves (Memorial Center, New York) have reached this conclusion on the basis of extensive studies of human breast cancer; and they have suggested that this be used as a guide in treatment. Patients with

estrogen-dependent cancers can be given remissions of many months' duration by castration and still further remissions by bilateral adrenalectomy. Patients whose cancers are not dependent upon estrogens probably are not benefited by either measure. Three such patients have been helped temporarily with cortisone in doses of 200 to 300 mg. a day, however. The researchers report that measurement of urinary calcium provides a sensitive index of the rate of tumor growth in patients with osteolytic metastases.

### ***Virus Therapy for Cancer . . .***

Newman and Southam (Memorial Center, New York) have reviewed fifty-seven cases of advanced cancer treated with a variety of viruses. They found at biopsy and autopsy that "no gross or microscopic morphological change attributable to any of the viruses inoculated was seen in any malignant cell." Viruses used included West Nile and its isolates—Egypt 101, Egypt 19, and Egypt 21—Illhéus, Bunyamwera, Newcastle-disease, Br I, Semliki Forest, two strains of dengue, R, mumps, and vaccinia. A few of the viruses produced lesions in non-neoplastic tissue, but, in most cases, the viruses were without effect, either good or bad.

### ***Hypnotherapy . . .***

Twelve advanced cancer patients were treated by hypnosis at the Sloan Hospital for Women and the Francis Delafield Hospital, New York, on the assumption that "more than any other group, the cancer patients need mental-physical therapy." Butler, who conducted the studies, observed subjective help—the relief of pain, anxiety, and organ dysfunction—in proportion to the depth of the trance. Those who easily entered a deep

trance derived substantial benefit. Others who entered only a light stage—and these included patients who had undergone lobotomy—obtained no help. Among the disadvantages of hypnotherapy: the few good subjects, the time required, the need for an experienced and well-trained hypnologist to govern each case, and the possibly deleterious effects on the health of the hypnologist. Advantages for patients able to enter a deep trance include: lessening of drug requirements; relief of pain; correction of organ dysfunction; reduction of depression, fear, and anxiety; prolongation of life; and "death . . . approached as is a night's sleep." The results indicate the need for future basic research into the physiological effects of hypnosis.

### ***Electronics in Cancer Research . . .***

Hyden and Bourghardt (Gothenburg) have designed an electronic machine to aid in cancer research. With it, structures and internal changes of cells can be studied with greater precision than before. Thin shavings of cellular growth consisting of up to 200 cells are divided into 12,000 "control points," the machine measuring and tabulating every point in four minutes.

### ***Cancer and Parental Age . . .***

Strong at Yale recently outlined a long-term program to determine whether the well-known relationship of cancer susceptibility to maternal age in animals exists also in human subjects. Such investigation should include (1) collection of controlled data on parental (especially maternal) age at birth of cancer patients, (2) the ordinal sequence of the family for cancer patients and the controls, and (3) vital statistics for brothers and sisters of cancer patients and the noncancerous controls.

protracted periods the high red counts, the tendency to leukemia, the high blood pressure, the viscous and too-coagulable blood, the burned-out marrows, and the threat of strokes and thromboses that characterize the disease.

Animal Studies: The undependability of clinical conclusions based upon animal studies was demonstrated again at the annual meeting of the American Association for Cancer Research. Shubik and Saffiotti (Chicago Medical School) disclosed that compounds considered noncarcinogenic or only slightly carcinogenic may produce highly malignant cancers. They spoke specifically about catalytically cracked oils with boiling-point ranges from 500° to 800° F. On the basis of extensive mouse studies, these fractions have not been considered dangerous. But the Chicago investigators found that they were highly carcinogenic to rabbits. Moreover, when the substances were applied with a cocarcinogen (in this case, doses of dibenzanthracene insufficient to induce tumors), a single application of the oil fractions produced mouse and rabbit cancers.

Human Study: Smith, Cooper, and Wynder (N. Y. U. and Memorial Center) reported that a human subject is serving as a guinea pig for the carcinogenic effects of cigarette-smoke fractions. The human volunteer, himself a scientist, has permitted his back and arms to be painted with suspect fractions. The test, of course, is not permitted to run long enough for actual cancers to develop. The scientists feel, however, that two or three criteria may indicate well in advance of malignant transformation whether the substances are carcinogenic. The early, pre-carcinogenic effects noted in induced skin cancers are: (1) loss of hair in the area of application, and (2) the loss of sebaceous glands. So far neither of these effects has been noted on the human skin, but a third phenomenon--the enlargement of cell nucleoli--has been observed. The test skin patches are removed surgically. The subject has stopped smoking.

# SCIENTIFIC SESSION

## Annual Meeting—American Cancer Society

October 18-19, 1954

Hotel Biltmore, New York, New York

### CANCER OF THE UTERUS

#### A CRITICAL APPRAISAL OF THE PROBLEM

##### Epidemiological Aspects

Incidence and Mortality of Uterine Cancer

Role of Heredity

Etiological Significance of Racial Studies

Other Epidemiological Studies: Absence of Occurrence of Uterine Cancer among Nuns

##### Detection of Early Uterine Cancer

The Vaginal Smear: Interpretation; Correlation of Cytology and Histology; Mass Screening for Uterine Cancer

The in Situ Problem

The Role of Cervical Biopsy in Definitive Diagnosis; Relationship of Cervical Leukoplakia to Carcinoma in Situ and to Invasive Cancer; Clinical Behavior of Untreated Carcinoma in Situ

##### Diagnosis of Cancer of the Corpus of the Uterus

Endometrial Aspiration and Biopsy

Preinvasive Carcinoma of the Endometrium

##### Treatment

The End Results of the Treatment of Uterine Cancer

Symposium: The Roles of Radiotherapy and Radical Surgery in Cancer of the Uterus

Symposium: Management of Urinary Tract Complications Following Radical Pelvic Surgery

##### Clinical Research in Uterine Cancer

Objective Criteria in the Selection of Patients for the Treatment of Carcinoma of the Cervix: Sensitization Response

Certain Spatial Anatomical Considerations in Pelvic Cancer

Correlation between the Granulosa-Theca Group of Ovarian Tumors and Endometrial Changes

Histochemical Reactions in the Normal Glands of the Uterine Cervix



## COMING MEDICAL MEETINGS

<b>Date</b> <b>1954</b>	<b>Association</b>	<b>City</b>	<b>Place</b>
Sept. 19-21	American Roentgen Ray Society	Washington, D. C.	Shoreham Hotel
Sept. 26- Oct. 2	World Medical Association	Rome, Italy	
Oct. 7-18	Pan Pacific Surgical Congress	Honolulu, Hawaii	
Oct. 11-15	American Public Health Association	Buffalo	Memorial Auditorium
Oct. 24-28	National Rehabilitation Association	Baltimore	Lord Baltimore Hotel
Oct. 25-30	National Gastroenterology Association	Washington, D. C.	Shoreham Hotel
Nov. 3-6	American Society Tropical Medicine and Hygiene	Memphis	
Nov. 8-11	Southern Medical Association	St. Louis	
Nov. 12-13	Inter-Society Cytology Council	Boston	Hotel Statler
Nov. 29- Dec. 2	American Medical Association Clinical Session	Miami	
Dec. 4-9	American Academy of Dermatology and Syphilology	Chicago	Palmer House
Dec. 13-17	American Congress of Obstetrics and Gynecology	Chicago	Palmer House
Dec. 26-31	AAAS Meeting	Berkeley	Univ. of Calif.

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